

Review

Lead Poisoning: Historical Aspects of a Paradigmatic “Occupational and Environmental Disease”

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Lead poisoning is one of the earliest identified and most known occupational disease. Its acute effects have been recognized from antiquity when this condition principally afflicted manual workers and slaves, actually scarcely considered by the medicine of that time. The Industrial Revolution caused an epidemic of metal intoxication, urging scientists and physician of that period to study and identify specific symptoms and organ alterations related to chronic lead poisoning. During the 20th century, the acknowledgment of occupational and environmental toxicity of lead fostered public awareness and legislation to protect health. More recently, the identification of sub-clinical effects have greatly modified the concept of lead poisoning and the approaches of medicine towards this condition. Nowadays, lead poisoning is rarely seen in developed countries, but it still represents a major environmental problem in certain areas. Consequently, it may appear as a paradigm of “occupational and environmental disease,” and the history of this condition seems to parallel the historical development of modern “Occupational and Environmental Health” as a more complete medical discipline.

Key Words: Lead poisoning, Occupational health, History

Introduction

Lead poisoning is a classic example of an occupational disease that is rarely seen in developed countries, although sub-clinical cases do occur. At the same time, lead intoxication from non-occupational sources has been, and still is, an environmental problem in several areas. Therefore, this condition could be properly looked upon as a paradigm of occupational and envi-

ronmental diseases. An analysis of the historical pathways that acknowledges its dual aspect could provide useful information on the connections between the workplace and the environment and, subsequently, on the origins and the development of the medical discipline now known as “Occupational and Environmental Health”.

Early Acknowledgments during the Pre-industrialized Era

Lead was one of the first metals humankind learned to use due to its ease of extraction and its ductility. Consequently, lead poisoning has already existed in antiquity [1]. The first clear descriptions of lead toxicity dated back to the second century BC, when the Hellenistic physician Nicander of Colophon identified the acute effects associated with high-dose exposure

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(paralysis and saturnine colic). However, in antiquity, chronic lead poisoning had not been well defined within a typical clinical frame, although the extensive use of this metal in different sectors does not exclude the presence of its toxic effects in the exposed population. The lack of interest towards this disease is not a surprise: in ancient times, those who were suffering from it were primarily artisans and, more broadly, workers of a low social class, whose conditions were not protected in general [2-4].

Since the first century BC, the use of lead in the Mediterranean basin has become more and more extensive due to the Romans' conquest of Britain, where the ores were particularly rich in lead, with a resulting increased availability of the metal itself [1]. A suggestive theory considered lead poisoning as the only contributory cause of the fall of the Roman Empire. In ancient Rome, water and sewage systems made a huge step forward in hygienic conditions and represented one of the essential factors to preventing the development of epidemic episodes in one of the greatest cities of that period [5]. The pipes were made of lead and consequently released metal salts in the transported water, resulting in high plasmatic levels of lead and thus shorter life expectancy, fertility disorders, and lower birth rates among those who drank that water, which meant those ruling the Empire [6]. Not coincidentally, many Roman emperors and patricians had reproductive problems and, to ensure an adequate offspring, had to turn to adoption. This theory has been partially challenged; lead poisoning would have derived from wine and not from water intake. The raw water came directly from the mountains and was therefore rich in calcium carbonate, which would have coated the pipes and formed a strong protection against the release of lead salts. Rather, it was the widely used wine preservative, the so-called *sapa*, a preparation of must, which was slowly cooked in lead containers [1]. This substance (which sees an etymological link with the Latin verb *sapio*, "to taste good") was also able to sweeten a poor quality wine, due to the content of lead acetate (also known as "lead sugar") produced during cooking [7].

The first medical hypotheses related to lead poisoning were formulated during the Renaissance. From this period on, the medieval artisans acquired the dignity of artists and their professional life became worthy of being studied and analyzed. The economic and cultural development in the fifteenth century drew workshop instructors and young apprentices into big cities, where they were engaged in the decorations of cathedrals and mansions of the new emerging masses, consisting of the commercial and financial middle-upper class [4]. Among workers, the greatest exposure to lead were most likely the painters, because of the use of lead-based colors, includ-

ing lead carbonate or cerussite (also known as "white lead"), a substance which was irreplaceable with the realization of the color "white" until the nineteenth century. Remarkable painters who became victims of lead poisoning may have been Piero della Francesca (c. 1416-1492), Rembrandt (1606-1669), and Francisco Goya (1746-1828) [8,9]. In addition, workers who engaged in other craft occupations were highly exposed to the metal. For example, in 1473, the German physician, Ulrich Ellenbog (1440-1499) pointed out to the goldsmiths and metalworkers the benefit of preventive measures to avoid poisoning and subsequent death arising from lead and mercury; he practically advised them "to keep the windows open" and "to cover the mouth with a rag" while working with metals [3].

In addition, during the Renaissance, there was a strong interest for metals, certainly influenced by alchemy; in this regard, we must mention the "De Re Metallica" (1556), written by the Saxon physician Georgius Bauer (better known as Agricola, 1494-1556), pioneer of the study of health problems amongst German miners. Considering the described scenario, the inclusion of lead, mercury, and arsenic in the pharmacopoeia of the German-Swiss physician and alchemist Paracelsus (1493-1541) might appear as a counter-current theory, but it has to be considered in compliance with his own principle, "dosis sola facit, ut venenum non fit" ("only the dose permits something not to be poisonous"). The theories of Paracelsus, while representing the basis for the future development of toxicology, were bitterly criticized and condemned by the scientific world at the time [10]. Two centuries later, in 1656, Samuel Stockhausen, a German physician openly against the Paracelsian medical model, advised the miners of the mining town of Goslar to avoid the aspiration of dusts, attributing the etiology of miners' asthma to the "noxious fumes" of a lead compound, the litharge [3]. In the following decades, the "Transactions of the Royal Society of England" published numerous articles about the risks of the manufacturers of white lead and glass. Meanwhile, Bernardino Ramazzini (1633-1714) identified all the lead processing techniques, used by potters, tinsmiths, and painters, as dangerous [7]. In his "De Morbis Artificum Diatriba" (1700), the Italian physician said about the workers in metal mines, "since [...] the use of metals is practically indispensable in all kinds of production, their health deserves attention and their illnesses ought to be studied so precautions and remedies may be offered." [11] In particular, Ramazzini stated about the potters who worked with lead, "first of all they suffer from palsied hands, abdominal colic, fatigue, cachexia, and they lose their teeth. It is, therefore, extremely rare that one can see a potter who does not have a lead-coloured, cadaverous looking face." [11]

Once the harmful effects of lead were evidenced in work-

ing populations, it took little to understand its non-occupational toxicity. The use of wine preservatives derived from the ancient *sapa* had persisted until the seventeenth century and it was a cause of recurring collective poisoning in some European areas. During that period, sudden outbreaks of saturnine colic periodically hit the French region of Poitou (*Colica Pictorum*) and some areas of the English countryside (the *Devonshire Colic* among cider drinkers). This intensely painful and debilitating disease, which frequently ended in death, was first described by Francis Citois (1572-1652) in 1639 [12]. During an epidemic of the “*Colica Pictorum*” in Ulm, the largest wine-trading center in Germany, Eberhard Gockel (1636-1703), one of the doctors of the city, gave forth his observations in “*De vini acidi per acetum lithargyri cum maximo bibentium damno dulcificatione*” (1697) or, he held the lead level in wine responsible for the clinical manifestation. For the first time in history, the consideration of the exposure to the metal was not only limited to an occupational concern, it was extended to the general population as well [12].

Chronic Lead Poisoning and Workers’ Protection during the Industrial Revolution

The epidemics of saturnine colic that occurred during the 17th century provided evidence for the acute effects of ingestion of this metal, even though some physicians did not initially acknowledge the etiology. For example, an epidemic of “*Devonshire colic*” lasted for many decades before being diagnosed as lead poisoning by Sir George Baker (1722-1809) in 1767, 70 years after the first acknowledgment by Gockel [13]. Only during the beginning of the 19th century have scientists clearly understood the mechanisms of lead poisoning by dietary intake. In his “*A Complete System of Medical Policy*,” the German hygienist Johann Peter Frank (1745-1821) had suggested avoiding water that flows in pipes of lead, reporting some cases of saturnine colic observed by him and other physicians [14].

While the acute effects of metal ingestion were well known, a full awareness of the chronic damages related to lead poisoning was ensured only in the 19th century. Indeed, during the Industrial Revolution, the intensive use of metals in manufacturing systems, at a time when preventive measures were likely to be poor, if existing at all, increased the number of workers afflicted by chronic metal poisoning and the consequent interest of physicians toward them.

In the “*Traité des maladies de plomb ou saturnines*” (1839), detailed signs and symptoms of chronic lead intoxication were reported by Louis Tanquerel des Planches (1810-1862)

through one of the first and most comprehensive studies on occupational disease [15]. By analyzing 1,200 cases of lead poisoning at the “*Hôpital de la Charité*” in Paris (renowned for its treatment of lead colic), the French physician noticed that the disease was more commonly present in those workers exposed to lead fumes rather than in those dealing with the solid form of the metal. Subsequently, the clinical picture took a different form. Anaemia was acknowledged early by René Laennec (1781-1826) in 1831, while the blue-purple line along the gum, a typical trait of the intoxication, was first described by the British neurologist Henry Burton (1799-1849) in 1840 [13,15]. Nineteen years later, Sir Alfred Baring Garrod (1819-1907) postulated a direct link between lead poisoning and gout, observing that one-third of his gout patients was plumbers and painters [16]. In his works, Tanquerel des Planches (1810-1862) also used the term “*encéphalopathie saturnine*” to indicate neuropsychiatric manifestations of lead poisoning, thus coining the medical term “*encephalopathy*” for the first time [17]. His observations on neurological complications of lead exposure were soon confirmed: Jean-Étienne Dominique Esquirol (1772-1840) in 1838 and then Daniel Hack Tuke (1827-1895) in 1880 provided cases of mental disorders resulting from chronic ingestion of minute amounts of lead [18]. From the beginning of the last century, the related nephropathy and hypertension and the effects on pregnancy outcome were all identified and described in the medical literature [13].

After these publications, the medical and the scientific communities, together with the political world, could no longer ignore the problem. Charles Turner Thackeray (1795-1833), whose work to improve the workers’ health conditions contributed to the development of the English legislation for workers, was perhaps the first to formulate the principle of removing and replacing harmful agents in the production cycle [5]. In the ceramic industry in particular, he recommended the replacement of lead-based glaze, and, if not possible, he advised a modification of the production process in order to minimize the workers’ exposure. In the following decades, in the UK, children were forbidden to work in white lead factories (1878). Later, the Parliament openly stood up on the issue, approving the Factories (Prevention of Lead Poisoning) Act (1883), which may be considered as the first worldwide legislative initiative to lessen the burden of a specific occupational disease [19].

Lights and Shadows during the Twentieth Century

Despite aforementioned social reforms at the end of the 19th century, the industrial development took little account of the

workers' health in most Western countries. For instance, the "White Lead (Painting) Convention", drawn up by the International Labour Office in Geneva in 1921 to ban the indoor use of lead paint, has never been ratified by the British Government, despite the efforts of many supporters [13]. Amid its advocates was Sir Thomas Morrison Legge (1863-1932), the first physician to be appointed as "Medical Inspector of Factories" and, together with the bacteriologist Sir Kenneth Weldon Goadby (1873-1958), they were among the authors of "Lead Poisoning and Lead Absorption" (1912), considered one of the most complete treatises on this topic [3]. The institution of the Labour Inspectorate in the UK had significantly contributed to reducing the number of cases of lead poisoning; thus, when the British Government refused to ratify the Geneva Convention in 1926, Legge resigned from his position in sign of protest [13].

However, one of the major determinants leading to the enactment of a specific legislation on lead paint at the international level was the identification of cases of lead poisoning among children at the beginning of the twentieth century. The observation of high blood lead levels among Australian children, and the contemporary presence of visual disturbances and ocular motility impairments (the so-called "ocular neuritis"), led the ophthalmologist John Lockhart Gibson (1860-1944) to believe that these symptoms were an expression of chronic poisoning from lead paint [20-22]. The affected children had lived and were living in houses where it was possible to find walls, gates, or railings that were freshly painted or, on the contrary, covered with old paint, easily scraped off and later ingested by the children, according to the so-called "hand-to-mouth behavior." Within the same household, the sick children were only the ones who had a habit of nail biting, thumb sucking, or eating with unwashed hands [20]. The first and best therapy was the removal of the young patients away from their own living environment: lead poisoning was in fact considered a "disease of the house." Gibson's observations were published in 1904; a series of studies, aimed to pursue his intuition further, were largely carried out in the US and his findings were supported. Similar cases were described in children who had been exposed to the metal through toys (coated with lead paint or even built with the metal itself), and with food coloring (for example, yellow lead was a common dye in sweets and candies) [21,22]. Some doctors put down this disorder not so much because of the lead content of the dyes, as to the pica (which is Latin for "maggie"), a behavioral disorder where one has the tendency to ingest any available object, or substance that is close by [23]. Despite these theories, which, however, did not explain the large frequency of cases, progress was made in the regulatory field; since the twenties of the last century, many

governments have begun to legislate in order to reduce the lead content in paints.

While it seemed that health problems related to lead paints were taken into consideration, Thomas Midgley Jr (1889-1944), together with other engineers of General Motors, detected the highly anti-knock effect of tetraethylene lead (TEL), when added to the gasoline. The discovery was fundamental for the construction of more and more powerful engines, contributing first, to the Allied victory in the Second World War, and later, to the maintenance of the US hegemony in the automotive industry until the early seventies [24]. By then, health problems among workers involved in the production of the additive substance were immediately reported. However, in spite of the data retrieved and offered by Alice Hamilton (1869-1970), a pioneer of studies on lead poisoning in the US, the economic depression and the years of war did not make it any easier for the US Government to take a sharp position on the issue [24].

The mid-20th century saw the introduction of the first preventive strategies in factories, such as the abolition of the use of lead, exhaust ventilation, wetting dusty processes, and personal protective equipment; at the same time, chelating agents came into use as a therapeutic tool against lead poisoning. In addition to these scientific and technological advances, several other odd preventive and therapeutic measures were applied, such as the practice of feeding the workers with a liter of milk per day [13]. Due to its "whiteness", milk was indeed looked upon as a purifying substance [25] and several scientists have confirmed this belief of postulating the role of calcium in retarding lead absorption [26].

As new methods for measuring lead in biological media continued developing in the late 1960s, the international debate focused on where the values of "safe" occupational exposure should lay and what is considered a "safe" exposure [13]. Only during the last decades have the identification of sub-clinical effects of lead intoxication led to an acknowledgement of the damages of the environmental pollution caused by the burning of TEL to the general population. In particular, children in the first months of life were found to be sensitive to soil pollution caused by lead in gasoline, because of their need to explore the world around them through their hands and their mouth, using the already mentioned hand-to-mouth behavior [27]. Therefore, in the industrialized countries, during the late eighties and early nineties, TEL was gradually replaced with benzene and the halving of the blood lead levels in the general population was documented soon after [7]. Consequentially, the media and part of the medical and scientific world have moved on and abandoned the issues related to lead intoxication. However, in 2000, childhood lead poisoning was revealed as a major

environmental public health problem in the US; since then, we have assisted in the development of a comprehensive set of lead poisoning prevention laws, which in return, reduced the environmental lead exposure significantly, with an economic benefit of USD 213 billion per year [28].

Meanwhile, research has flourished to address better the health consequences of environmental low-level chronic exposure to lead in children, as with adults. Results of a recent review by Bellinger have shown that scientists have yet to place a threshold to identify the level below which lead exposure does not result in an intelligence quotient loss in children (considered the most sensitive endpoint) and there are still controversies on the shape of the dose-response curve. Neuro-imaging techniques appear to support the existence of organic damage and the emergence of different types of behavioral disorders in chronically exposed children corroborates the evidence of lead-induced effects at doses below 10 g/dL. Similarly, in adults, all-cause mortality, renal impairment, cardiovascular disease (particularly hypertension), infertility, and neurological disorders have been associated with low-level non-occupational chronic exposure to lead [29].

Moreover, in light of the newly evolved concept of poisoning and the acknowledgement of the effects of chronic exposure to micro-doses, in the last years, the international scientific community have begun to study the genetic, epigenetic, and carcinogenic effects of lead in humans and animals [30-35].

Lead Poisoning and the Development of Occupational Health

The history of lead poisoning traces the origin and the development of "Occupational Health" as a medical discipline. In pre-industrialized era, workers' health conditions were not taken into account by the contemporary physicians until the Renaissance, when manual workers acquired the dignity of artists and began to be more considered and protected. During the Industrial Revolution, the poor work conditions caused an epidemic of occupational diseases, therefore giving rise to the birth of "Occupational Medicine." Based on a clinical approach, this specialty gave a detailed and good description of specific alterations of each organ due to occupational toxins (in particular, the abdominal, neurological, cardiovascular, and renal complications of lead poisoning). Meanwhile, the first specific legislations for workers' safety were enacted by several governments, initially protecting only vulnerable categories at work (i.e., children and women), and then extending preventive measures to all the workers. During the 20th century, the

development of Industrial Hygiene supported several technical improvements in industry, thus reducing exposure to toxins. Periodical surveillance of workers, mandatory in several countries, began to be based on biochemical and not merely clinical examinations. In the last decades, the acknowledgment of sub-clinical effects changed the concept of "poisoning" greatly and the philosophy of occupational medicine itself. In particular, the discipline evolved towards a broadened concept of "Occupational Health" and began to investigate also non-occupational exposures and clinical/sub-clinical effects of toxins on the general population [36]. Moreover, Occupational Health and Safety professionals were charged with managing environmental protection. In the early 1990s, for example, the Board of Directors at the "American College of Occupational Medicine" proposed adding the word "Environmental" to the title of their discipline [37]. In this way, a new discipline "Occupational and Environmental Health" emerged, aimed at studying those diseases caused by noxious agents in both living and working spaces, such as "lead poisoning," which is a paradigm of these conditions. The parallels between the history of lead poisoning and the development of "Occupational Health" are also evidenced in new emerging economies, even if for a shorter temporal period [38].

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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